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Community Water Fluoridation Exposure: A Review of Neurological and Cognitive Effects – A 2020 Update

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Abbreviations

ADHD	Attention deficit hyperactivity disorder
BMI	Body mass index
CADTH	Canadian Agency for Drugs and Technologies in Health
CHMS	Canadian Health Measures Survey
CI	Confidence interval
CRT-RC2	Combined Raven's Test for Rural China, 2nd edition
CWF	Community water fluoridation
FSIQ	Full Scale IQ
FT3	Free triiodothyronine
FT4	Free thyronine
HOME	Home Observation for Measurement of the Environment
HTA	Health technology assessment
IQ	Intelligence quotient
MIREC	Maternal-Infant Research on Environment Chemicals
MUF	Maternal urine fluoride
OR	Odds ratio
PIQ	Performance IQ
ppm	part per million
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
SD	Standard deviation
SDQ H/I	Strengths and Difficulties Questionnaire Hyperactivity Inattention
TSH	Thyroid stimulating hormone
TT3	Total triiodothyronine
TT4	Total thyronine
UF_{SG}	Urine fluoride adjusted for specific gravity
VIQ	Verbal IQ
WPPSI-III	Wechsler Preschool and Primary Scale of Intelligence, Third Edition

Context and Policy Issues

In Canada, community water fluoridation (CWF) is the process of monitoring and controlling fluoride levels (by adding or removing fluoride) in the public water supply to reach the optimal level of 0.7 mg/L or part per million (ppm) and not to exceed the maximum concentration of 1.5 ppm, as recommended in the 2010 *Health Canada Guidelines for Drinking Water Quality*.[1] CWF has been identified as a cost-effective method of delivering fluoride to the population and reducing dental caries in children and adults.[2,3] The Centers for Disease Control and Prevention recognized CWF as one of 10 great public health achievements of the 20th century because of its contribution to the prevention of tooth decay and improvement in oral health over the past 70 years.[4] CWF is endorsed by over 90 national and international governments and health organizations around the world.[5,6]

Despite the endorsement of governments and health organizations, and a large body of empirical evidence on the preventive effect of CWF on dental caries, a number of municipalities across Canada have not implemented or have discontinued water fluoridation.[7] In 2017, 38.7% of the Canadian population were exposed to community water systems having recommended optimal fluoride levels to protect their teeth.[7] Different factors have contributed to CWF cessation including concerns about the potential harmful side effects of water fluoride to human health, including fluorosis, skeletal fractures, cancer, reproduction and development, thyroid function, and neurological development and cognitive function.[1]

Multiple studies have been published showing that exposure to higher levels of fluoride in drinking water may be associated with lower intelligence among children.[8-11] However, the applicability of the findings from those studies to the Canadian context is unlikely given they were conducted in rural and endemic areas and areas of low socioeconomic status in countries, such as China, India, Iran, or Mexico, which also include other sources of fluoride such as fluoridated salts or naturally occurring water fluoride levels that are many folds higher than the current Canadian levels.[8-11] Multiple methodological limitations were identified in those studies including insufficient control for important confounding factors and low quality study design.[12,13]

The CADTH CWF Review of Dental Caries and Other Health Outcomes reviewed studies from countries with comparable water fluoride levels and socioeconomic parameters, and found no evidence for an association between water fluoridation at recommended Canadian levels and intelligence quotient (IQ) or cognitive function.[12] A 2019 CADTH Rapid Response report[14] reviewed a prospective cohort study conducted in Canada, in which the study authors concluded that exposure to higher levels of fluoride during pregnancy is associated with lower full-scale IQ scores in children aged 3 to 4 years.[15] However, the CADTH review found the study findings did not support its conclusion, as the mean of Full scale IQ was not different between children from fluoridated and non-fluoridated areas, and the effect was only significant when the analysis was restricted to boys.[14] There appear three recently published studies in the literature examining the association between fluoride exposure and IQ and attention deficit hyperactivity disorder (ADHD) in children. One study was conducted in China,[16] and two studies were from Canada.[17,18] The appearance of those studies prompted CADTH to conduct an updated review on the same topic.

The aim of this report is to update the previous CADTH reports[12,14] by reviewing recent evidence on the effects of fluoride exposure through CWF at levels that are relevant to the Canadian context on the neurological or cognitive development in children and adolescents less than 18 years of age.

In this report, gender-neutral language has been used where possible in order to be inclusive of all gender identities. When reporting results from the published manuscript, gender-neutral language was not used in order to be consistent with the terms used in the source material.

Research Question

1. What are the neurological or cognitive effects of community water fluoridation, compared with non-fluoridated or different fluoride levels in drinking water, in individuals less than 18 years of age?

Key Findings

This review included one prospective cohort study and two cross-sectional studies examining the effect of fluoride exposure on intelligence quotient (IQ) and attention deficit hyperactivity disorder (ADHD) diagnosis in children. These studies are of low quality due to high risk of bias and multiple limitations.

The prospective cohort study conducted in Canada examined fluoride exposure (determined by fluoridation status and fluoride intake from formula) over the first six months of feeding and IQ in children aged 3 to 4 years. It was found that an increase of 0.5 mg/L of tap water fluoride levels was associated with 9.3 points and 6.2 Performance IQ points decrease in formula-fed group and breastfed group, respectively. An increase in 0.5 mg fluoride intake from formula per day was associated with a statistically significant decrease in 8.76 points of Performance IQ.

The cross-sectional study conducted in China examined the association between fluoride exposure (water fluoride levels from 0.2 to 3.9 mg/L in the endemic and non-endemic areas) and IQ in children aged 7 to 13 years in relation to thyroid hormones. At water fluoride levels of 0.7 to 1.0 ppm, the study found no significant difference in IQ scores or thyroid hormone levels compared to water fluoride levels of less than 0.7 mg/L. A regression analysis including all water fluoride levels showed a statistically significant, but rather small decrease in IQ scores; 1.6 points for every 1 mg/L water fluoride, or 1.2 points for every 1 mg/L urinary fluoride.

The cross-sectional study conducted in Canada examined the association between fluoride exposure (determined by urinary fluoride, city fluoridation status and tap water fluoride levels) and ADHD in children aged 6 to 17 years. The results showed no significant association between urinary fluoride and ADHD diagnosis, or between urinary fluoride and the Strengths and Difficulties Questionnaire Hyperactivity Inattention (SDQ H/I) subscale score. Water fluoride levels and CWF status were positively associated with ADHD diagnosis and SDQ H/I subscale score. Every increase of 1 mg/L of tap water fluoride was associated with a 6.1 times higher odds of ADHD diagnosis and an increase of 0.31 points in the SDQ H/I subscale score. Similarly, children living in the fluoridated areas had 1.5 times higher odds of ADHD diagnosis and an increase of 0.11 points in the SDQ H/I subscale score. Children of older age (i.e., 14 years and over) were more likely to be affected compared to those of younger age (i.e., 9 years and under).

Considering multiple limitations of the included studies (e.g., insufficient control of confounding factors, potential misclassification of exposure, and inadequate study design), it is difficult to interpret their findings and generalize them the Canadian context. Collective evidence from the recent CADTH reports and the current review indicates there is insufficient evidence to conclusively conclude that fluoride exposure at the Canadian water fluoride levels (optimum at 0.7 mg/L) affects neurological development in children and adolescents in Canada.

Methods

Literature Search Methods

This report makes use of a literature search strategy developed for a previous CADTH report. For the current report, a limited literature search was conducted by an information specialist on key resources including Medline via OVID, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were water fluoridation and children (<18 years). No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2019 and October 1, 2020. The search dates were selected to identify information published subsequent to a previous search for the CADTH report Community Water Fluoridation Exposure: A Review of Neurological and Cognitive Effects.[14]

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Persons less than 18 years of age (including *in utero)*
Intervention	Natural or artificial water fluoridation (range between 0.4 ppm to 1.5 ppm with the optimal level being 0.7 ppm)
Comparator	No water fluoridation, low fluoride level (< 0.4 ppm), or different fluoride levels in drinking water
Outcomes	Neurological (e.g., neurotoxicity) or cognitive outcomes (e.g., Intelligence Quotient)
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, and non-randomized studies

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria in Table 1and if they were published prior to 2019. Primary studies were also excluded if they had been included in the recent CADTH Rapid Response report on CWF exposure.[14]

Critical Appraisal of Individual Studies

The methodological quality (i.e., internal and external validity) of the included non-randomized study was assessed using the National Institute for Health and Care

Excellence (NICE) checklist.[19] Summary scores were not calculated for the included study; rather, a review of the strengths and weaknesses were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 144 citations were identified in the literature search. Following screening of titles and abstracts, 121 citations were excluded and 23 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search. Of the 23 potentially relevant articles, 20 publications were excluded for various reasons, while three non-randomized studies met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA flowchart[20] of the study selection.

Summary of Study Characteristics

The detailed characteristics of the included studies[16-18] (Table 2) are presented in Appendix 2.

Study Design

One prospective cohort study[17] and two cross-sectional studies[16,18] were identified.

The prospective cohort study by Till et al. 2020[17] used the same data set as the study in Green et al. 2019,[15] which looked at the association between maternal fluoride exposure during pregnancy and children's IQ. Data were from the Canadian Maternal-Infant Research on Environmental Chemicals (MIREC) program. Till et al. 2020[17] examined the association between infant fluoride exposure through feeding status and children's IQ. The program recruited 2,001 pregnant persons from ten Canadian cities between 2008 and 2011 to participate in a longitudinal pregnancy cohort study. A subset of mother-child pairs (n = 610) from the original cohort were recruited from six cities (Vancouver, Toronto, Hamilton, Halifax, Kingston, Montreal) to participate in the developmental follow-up phase. Mothers of children between 30 to 48 months completed an infant-feeding questionnaire. Those who breastfed ≥ 6 months were put in the breastfeeding group; those who reported introducing formula within the first 6 months (never breastfed or partial breastfeeding) were put in the formula feeding group. Infant fluoride exposure was determined using the mother's postal code that linked to a water treatment plan with known water fluoride levels over the first 6 months of child life. Fluoride intake from formula during the first year was estimated using a non-validated method (i.e., a mathematical equation designed by the authors). Fetal fluoride exposure was estimated from maternal urinary fluoride adjusted for specific gravity. Linear regression was used to assess differences in child IQ by water fluoride concentration with controlling of covariates in two models. The first model looked at the association between IQ scores and water fluoride concentration by feeding status. The second model estimated association between fluoride intake from formula and child IQ. The covariates were child's sex and age at testing, maternal education, maternal race, second-hand smoke in the home, and quality of child's home environment.

The cross-sectional study by Wang et al. 2020[16] was conducted in the rural areas of Tianjin City, China to examine the association between fluoride exposure and IQ in relation with thyroid function in children aged 7 to 13 years. The study participants were selected using a stratified and multistage random sampling approach. Water samples were collected randomly from the public water supplies in each village, and urine samples were collected in the early morning before breakfast. Fluoride contents in the water and urine were measured using fluoride ion selective electrode. Five thyroid hormones such as total triiodothyronine (TT3), total thyronine (TT4), free triiodothyronine (FT3), free thyronine (FT4) and thyroid stimulating hormone (TSH) were measured using chemiluminescent microparticle immunoassay. Multivariable linear regressions with adjustment of covariates were used to estimate the changes in thyroid hormones and IQ scores for every 1 mg/L increase in water fluoride and urinary fluoride concentrations. The selected covariates were age, gender, body mass index (BMI), paternal education level, maternal education level, household income, and low birth weight. Benjamin-Hochberg false discovery rate procedure was applied to address multiple testing corrections.

The cross-sectional study by Riddle et al.,[18] used data from the Canadian Health Measures Survey (CHMS); Cycle 2 (2009 to 2011) and Cycle 3 (2012 to 2013) to examine the association between fluoride exposure and attention outcomes of Canadian youth 6 to 17 years of age. Logistic regression models were used to examine the associations between each fluoride exposure (i.e., UF_{SG}, CWF status, tap water fluoride level) and ADHD. Linear regression models were used to examine the associations between each fluoride exposure (i.e., UF_{SG}, CWF status, tap water fluoride level) and the Strengths and Difficulties Questionnaire Hyperactivity Inattention (SDQ H/I) subscale score. Selected covariates were sex, age, ethnicity, BMI, level of education obtained by either parent, total household income, exposure to cigarette smoke at home, and level of blood lead.

Country of Origin

The studies were conducted by authors in Canada and the US,[17,18] and in China.[16]

Patient Population

Of the 610 recruited mother-child pairs, the study by Till et al.[17] initially included 601 mother-child pairs who completed all testing, but only 398 (67.3%) mother-child pairs who reported drinking tap water, had water fluoride data and complete covariate data were selected for analyses (breast-fed, n = 200; formula-fed, n = 198). Mother mean age was 32 years with no significant difference between fluoridation status or feeding status. Compared with the formula-fed group, the breastfed group had significantly higher proportion of mothers with higher education, higher proportion of mothers who had married or common-law, and higher in the Home Observation for Measurement of the Environment (HOME) total score. Child mean age at the time of IQ testing was 3.4 years (range 3 to 4 years) with no significant difference between feeding status. The proportions of homes with second-hand smoke, gestational age and birth weight were balanced between feeding status and between fluoridation status.

The study by Wang et al.[16] recruited 571 children, aged 7 to 13 years, from the endemic and non-endemic areas in Tianjin, China. The basic characteristics were reported for the total population, but were not reported for each exposure group. Children's mean age was 9.8 years, with balance in numbers of boys and girls. The average years of residence was 10.12 years, and 4.6% of children had low birth weight. The majority of father (81.4%) and mother (83.9%) education level was middle school or below.

In the study by Riddell et al.,[18] three samples of children 6 to 17 years old were used in the analyses, representing three types of fluoride exposure (i.e., based on urinary fluoride, CWF status, water fluoride levels). Sample 1 (N = 1,877) included children from cycles 2 and 3 who had urinary fluoride measurement. Sample 2 (N = 1,722) included children from cycles 2 and 3 who had known city fluoride status (n = 932 in fluoridated area; n = 790 in non-fluoridated area). Sample 3 (N = 710) included children from cycle 3 who primarily drank tap water with known water fluoride levels. Child mean age at interview was 11.3 years and was similar across all three samples. The numbers of boys and girls were nearly equal in all samples. About 80% children lived 3 years or more and 20% lived less than 3 years in the areas. About half number of parents had University or higher education level.

Exposures

The study by Till et al.[17] examined fluoride exposure at fluoridated and non-fluoridated areas, where the mean water fluoride levels (SD) were 0.59 (0.07) mg/L and 0.13 (0.06), respectively. Other fluoride exposure variables included infant fluoride intake from formula or from breastfed milk measured using a non-validated formula and fetal fluoride exposure determined by maternal urinary fluoride (MUF).

The study by Wang et al.[16] examined fluoride exposure at higher levels of water fluoride (i.e., 0.70 to 1.00 mg/L; 1.00 to 1.90 mg/L; > 1.90 mg/L) compared to lower water fluoride level (i.e., < 0.7 mg/L). Water fluoride concentration ranged from 0.2 mg/L to 3.9 mg/L; the mean value (SD) was 1.39 (1.01) mg/L. The comparison between water fluoride concentrations of 0.70 to 1.00 mg/L and < 0.7 mg/L was more relevant and in scope with the PICO in this review. However, findings from linear regression analyses where all fluoride concentrations were included were also presented in this report.

The study by Riddell et al.[18] examined fluoride exposure at fluoridated and non-fluoridated areas, where the mean water fluoride levels (SD) were 0.49 (0.22) mg/L and 0.05 (0.06) mg/L, respectively. Exposure to fluoride was determined by urinary fluoride adjusted by specific gravity (UF_{SG}), CWF status, and tap water fluoride level.

Outcomes

In the study by Till et al.,[17] the intelligence outcomes were full scale IQ (FSIQ), a measure of global intellectual functioning, verbal IQ (VIQ), a measure of verbal reasoning, and performance IQ (PIQ), a measure of non-verbal reasoning, spatial processing and visual-motor skills. The outcomes were assessed using the Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III).[21] The WPPSI-III contains different sets of subtests for two age bands (from 2 years and 6 months to 3 years and 11 months, and from 4 years and 0 months to 7 years and 3 months). For children in the first age range, FSIQ, VIQ and PIQ scores are obtained from four core subtests. Seven core subtests are for children in the second age range. An overall intelligence score between 90 to 109 with a standard deviation of 15 is considered as average.[22]

The outcome in the study by Wang et al.[16] was IQ scores assessed using a combined Raven's Test for Rural China, 2nd edition (CRT-RC2). The test assessed a range of intelligence functions without depending on language skills and had 72 questions in six sets of 12.[16] The examiners were blinded to the participants' drinking water fluoride levels.

The outcomes in the study by Riddell et al.[18] were SDQ H/I subscale score and Attention Deficit Hyperactive Disorder (ADHD) diagnosis. The SDQ has 25 items with a 3-point response scale (0 = not true; 1 = somewhat true; 2 = certainly true).[18] These items are grouped into five subscales: emotional problems, conduct problems, hyperactivity-inattention, peer problem, and prosocial behaviour.[18] Scores in each subscale range from 0 to 10.[18] ADHD was diagnosed by doctors. Questions for ADHD diagnosis differed between cycle 2 and cycle 3. In cycle 2, the following question was asked: *"Do you have a learning disability"*, if Yes, then specify type of learning disability: 1) ADD; 2) ADHD; 3) Dyslexia; 4) other. In cycle 3, Children were asked whether they "*received physician-diagnosed ADHD*", and if Yes, which subtype. Parents or guardians provided information for children age 6 to 11 years. Children 12 to 17 years completed the questionnaire and answered the question.

Summary of Critical Appraisal

The detailed quality assessments of the included studies[16-18] (Table 3) are presented in Appendix 3.

The study by Till et al.[17] used the same cohort and methods as in their previous study examining the association between fetal fluoride exposure and IQ in children aged 3 to 4 years.[15] Therefore, this study had the same strengths and weaknesses in methodology as the previous one that had been reviewed by CADTH.[14] The population was well described as it was recruited from six Canadian cities. However, it was unclear how six out of 10 cities were chosen as the recruitment of individuals, clusters or areas was not defined. There was a risk of selection bias as the method of selection of participants from the eligible population was not described and there was no report on the percentage on selected individuals or clusters who agree to participate. The study considered only 610 out of 2,001 pregnant persons from the MIREC program, and only 398 mother-child pairs were included in the analyses, representing 19% of the eligible birth cohort. Infant fluoride exposure was determined by the CWF status with known water fluoride levels over the first six months of child life and by fluoride intake through feeding status using a non-validated method. There was some attempt to minimize the possibility of recall and response bias that the authors compared the information reported by mothers at time of classification by feeding status (i.e., children aged between 30 and 48 months) with information of a subset of mothers at an earlier visit (i.e., children aged between 6 and 8 months). However, only 11% of the sample were available for verification. The study tried to link infant fluoride exposure during the first year of life through drinking tap water and IQ in children of 3 to 4 years later, by assuming that all mothers in the formula fed group used only tap water to reconstitute the formula. The study assumed that fluoride intake was totally from tap water and did not take account for fluoride content derived from formula into the estimation. Moreover, there was a gap between first year of feeding and intelligence assessment time (i.e., children aged 3 to 4 years), during the time of which fluoride exposure and fluoride intake were unknown. Covariates such as child's sex and age at testing, maternal education, maternal race, smoke in the home, and quality of child's home environment were identified and adjusted in the regression analysis. Potentially missing confounding factors included residential mobility, socioeconomic status, marital status, paternal education, maternal and paternal IQ, alcohol consumption, differences in nutritional contents in breast milk and formula, first-born, low birth weight, and children fluoride exposure and other chemical exposure between the period of weaning and the time point of intelligence assessment. The study did not take into account that breast feeding was associated with higher IQ in children compared with those receiving formula feeding.[23] As the IQ of children may change during development, the intelligence tests should be performed at multiple time points, rather than at only one time point (i.e., 3 to 4 years), and the exact children's age at the test was not considered in the analysis. The children's intelligence was assessed using WPPSI-III, which provides different sets of subtests for the 2 years 6 months to 3 years 11 months age group and the 4 years to 7 years 3 months age group. Therefore, the reliability of the test used for children between 3 and 4 years was unclear. The knowledge of the classification of exposure and feeding status might have affected the scoring of children's IQ as there was no indication that the assessors conducting the tests were blinded. The results from all recruited participants were not reported and it was unclear if excluding children due to missing data could affect the findings. The study did not report if it performed any sample calculation to obtain sufficient power to detect an intervention effect. The sample size was relatively small and the numbers of participants in the fluoridated areas were relatively smaller than those living in the non-fluoridated areas. For instance, among formula-fed group, only 68 participants were in the fluoridated areas compared with 130 participants in the non-fluoridated areas, and among breastfed group, only 83 participants were in the fluoridated areas compared with 117 participants in the non-fluoridated areas. The study used linear regression to assess differences in children's IQ by water fluoride concentration and fluoride intake from formula. However, the association of confounders with IQ were not presented separately for each confounder, and all the influential confounders were not identified and included in the multivariable analysis. It was unclear if the association between fluoride exposure and children's IQ was meaningful as the R-squared values for linear regression were not reported. Moreover, the study did not conduct multiple testing adjustment to account for multiplicity. With the P value of 0.05, there was a high likelihood of detecting false positive finding with multiple statistical tests.[24] It is unclear if it is valid to divide the regression coefficients by 2 for the prediction of IQ difference per 0.5 mg/L water fluoride or 0.5 mg fluoride in the formula. In summary, internal validity of the study results may be compromised due to risk of bias from selection of participants, classification of intervention, confounding, missing data, measurement of outcomes, and statistical analysis. Although the study was conducted in Canada, the findings could not be generalizable to the entire Canadian population due to the aforementioned study limitations.

In the study by Wang et al.,[16] the source of population and the method of selection of participants were well described. Resident children, aged 7 to 13 years, were recruited from endemic and non-endemic fluorosis rural areas in Tianjin, China. The whole district was divided into high fluoride areas and normal fluoride areas according to the upper limit of 1 mg/L. The authors stated that none of the study sites was exposed to neurotoxins known affecting IQ such as arsenic, lead or mercury in drinking water, but data were not shown. The study did not consider for the presence of those toxins derived from other sources such as foods. Study participants were selected using a stratified and multistage random sampling approach. However, there was risk of selection bias as no report on the percentage of selected individuals or clusters who agreed to participate was provided. Fluoride exposure was assessed by fluoride content in the water and from children's urine. The study had a clearly pre-defined level of fluoride exposure that was considered as low or high at start of the study with the upper limit of 1 mg/L. Water fluoride levels were divided into four quartiles: Q1 (≤0.7 mg/L), Q2 (0.70 to 1.0 mg/L), Q3 (1.00 to 1.90 mg/L), Q4 (>1.90 mg/L). The study reported that children who were not long-term residents of the area were excluded, but did not provide a definition about long-term. No further attempt was reported to minimize selection bias. Participants' characteristics were reported for total study population, but not at the group level. Therefore, it is unclear if the characteristics were balanced among groups. Evidence for the hypothesis that thyroid hormones might play a role in the association between fluoride exposure and children's intelligence was based on animal and human studies conducted with high levels of fluoride. The study assumed that drinking water was the sole source of fluoride exposure without considering other sources such as foods and oral hygiene products. The analyses were adjusted for selected confounders such as age, gender, BMI, paternal education level, maternal education level, household income, and low birth weight. Potential missing confounding factors were residential mobility, water improvement plants (whether fluoride, lead, or arsenic removed from drinking water), breastfeeding, other sources of fluoride (e.g., foods, oral hygiene products), parents' socioeconomic status, parental IQ, first-born, intake of iodine, and exposures to other chemicals such as lead, mercury or arsenic that are known to affect neurological development in children. The outcome measures and procedures were reliable. The CRT-RC2 was used to evaluate the IQ in each child, and the examiners were blinded to the fluoride exposure status. It was unclear if follow-up time was similar in all participants, and whether they all lived in the areas since birth. The study did not perform any sample calculation to obtain sufficient power. Two measures of fluoride exposure (water fluoride and urinary fluoride) were used in the analyses for the association between fluoride exposure and children's IQ. However, urinary fluoride was not adjusted by urine creatinine or specific gravity to account for dilution, and fluoride levels were measured in early morning spot urine samples instead of 24-hour urine collections. The analytical methods were appropriate as multivariable linear regressions were used to estimate the changes in THs and IQ scores for every 1 mg/L increase in water fluoride and urinary fluoride concentrations, with the adjustment of covariates. The study also performed multiplicity adjustment by applying the Benjamin-Hochberg false discovery rate procedure to address multiple testing corrections. However, it was unclear whether the associations were meaningful as R-squared values for linear regression were not reported. Overall, the internal validity of the study may be compromised by potential bias from selection of participants, incomplete control of confounding factors, and outcome assessments. The findings of the study are likely not relevant to the Canadian context as the study was conducted in China, where water fluoridation, socioeconomics and healthcare system are different.

In the study by Riddell et al.,[18] data source was from the Canadian Health Measures Survey (CHMS); Cycle 2 (2009 to 2011) and Cycle 3 (2012 to 2013). Three samples of youth 6 to 17 years of age representing three types of fluoride exposure (i.e., urinary fluoride, city fluoridation status and tap water fluoride levels) were included in the analyses. However, there was a risk of selection bias as the method of selection of participants from the eligible population was not described, and there was no attempt to minimize selection bias. Other sources of fluoride exposure such as foods and oral hygiene products were not considered. Evidence for the hypothesis that childhood fluoride exposure was associated with adverse behavioral outcomes in children was drawn from animal and human studies with high water fluoride levels. Covariates included in regression model were sex, age, ethnicity, BMI, level of education obtained by either parent, total household income, exposure to cigarette smoke at home, and level of blood lead. Potential missing confounders included residential mobility, other sources of fluoride, water improvement plans, breastfeeding, hereditary factor, other sources of fluoride, parental IQ, socioeconomic status, alcohol consumption, first-born, low birth weight, and exposure to other chemicals. The authors discussed that genetic component (70% to 80%), environmental exposures to heavy metals and chemicals, and nutritional factors play a major role in the development of ADHD, but the study did not adjust for those risk factors. The outcome measures and procedures appeared to be reliable; however, urinary fluoride was measured from urine spot sample, instead of 24-hour urine, and self-reported on ADHD diagnosis was likely subjected to reporting bias. The study selected children who lived in the areas for three or more years but did not show whether there was any difference in the residing time between exposure and comparison groups. Misclassification might occur due to changes in areas of residency. Included participants should be required to have lifetime exposure to fluoride instead of three or more years of exposure only. The follow-up time might not be meaningful as the outcomes were assessed at only one time point in a population with wide age range (i.e., 6 and 17 years). With respect to statistical analyses, the study did not report any sample calculation to obtain sufficient power, R squared values for linear regression were not reported, and adjustment for multiplicity due to multiple statistical testing was not performed. Overall, the internal validity of the study results may be compromised by risk of bias due to selection of participants, misclassification, improper control of confounding factors, missing data, and measurement of outcomes. Although the study was conducted in Canada, the methodological limitations of the study preclude the generalizability of the findings to the Canadian population.

Summary of Findings

The main findings and authors' conclusions of the included studies[16-18] (Table 4) are presented in Appendix 4. The results of each study are presented separately.

1) The study by Till et al. 2020[17] examined the association between fluoride exposure from infant formula and children's IQ.

FSIQ scores

Among breastfed group, the mean FSIQ score of children aged 3 to 4 years living in the fluoridated areas was not significantly different compared to that of those living in the non-fluoridated areas (109.9 ± 12.4 versus 109.9 ± 13.6). Similar results were found among formula-fed group (106.1 ± 15.8 versus 106.8 ± 13.5). Comparing between breastfed and formula-fed, the mean FSIQ scores of children in the formula-fed group was significantly lower than that in breastfed group (P = 0.03) by about 3 points in both fluoridated and non-fluoridated areas.

VIQ scores

Among the breastfed group, the mean of VIQ score of children living in the fluoridated areas was significantly higher by about 5 points compared to that of those living in the non-fluoridated areas (115.1 ± 11.3 versus 110.4 ± 12.4; P = 0.02). There was no significant difference in VIQ scores among formula-fed group who lived either in the fluoridated or non-fluoridated areas (110.9 ± 14.9 versus 107.1 ± 13.3). Comparing between breastfed and formula-fed, VIQ of children in formula-fed group was significantly lower than those in the breastfed group (P = 0.00) by about 5 and 3 points in both fluoridated and non-fluoridated areas, respectively.

PIQ scores

Among breastfed group, the mean PIQ score of children living in the fluoridated areas was not significantly different compared to that of those living in the non-fluoridated areas (102.0 ± 15.2 versus 105.6 ± 15.8). However, among the formula-fed group, the mean PIQ score of children living in the fluoridated areas was significantly lower by about 6 points compared to that of those living in the non-fluoridated areas (99.7 ± 15.1 versus 105.6 ± 13.4; P < 0.001). Comparing between breastfed and formula-fed, there was no significant difference in PIQ irrespective to the city fluoridation status.

Taken together, the results of the IQ assessment showed children receiving formula-feeding had significantly lower FSIQ scores and VIQ scores, and had no significant difference in PIQ compared to children receiving breast-feeding, irrespective to fluoridation status.

Association between water fluoridation concentration by feeding status and IQ scores

In the formula-fed group, an increase in 0.5 mg/L fluoride concentration was associated with a significant decrease in 4.40 points of FSIQ (95% CI – 8.34 to – 0.46; P < 0.05), a significant decrease in 9.26 points of PIQ (95% CI – 13.77 to – 4.76; P < 0.05), and no significant change in VIQ. After adjusting for MUF to control for fetal exposure, the association between water fluoride concentration and FSIQ was no longer significant.

In the breastfed group, an increase in 0.5 mg/L fluoride concentration was associated with a significant decrease in 6.19 points of PIQ (95% CI – 10.45 to – 1.94; P < 0.05), without any significant change in FSIQ or VIQ. Adjusting for MUF produced similar results.

Association between fluoride intake from formula and IQ scores

An increase in 0.5 mg fluoride intake from formula per day was associated with a significant decrease in 8.76 points of PIQ (95% CI – 14.18 to – 3.34; P < 0.05), without any significant change in FSIQ or VIQ. Adjusting for maternal urinary fluoride produced similar results; PIQ was -7.62 (95% CI -13.64 to – 1.60; P < 0.05).

In summary, the study by Till et al. 2020[17] found that fluoridation status or fluoride intake from formula was associated with a statistically significant decrease in PIQ scores, but not FSIQ or VIQ scores in both the breastfed group and the formula-fed group. For every increase in 0.5 mg/L tap water fluoride concentrations (i.e., approximate difference in fluoride levels between fluoridated and non-fluoridated areas), PIQ scores dropped by 6.3 points and 7.9 points in the breastfed group and formula-fed group, respectively. For every increase in 0.5 mg fluoride intake from formula per day, PIQ scores dropped by 7.6 points.

2) The study by Wang et al.[16] examined the associations between fluoride exposure and children's intelligence in relation to thyroid function.

Assessment of IQ in children aged 7 to 13 years

The mean IQ score of the total population was 106.74 ± 11.82, ranging from 75 to 145. About 80% of the population had IQ scores between 90 to 120.

Fluoride exposure

The mean fluoride concentrations in drinking water was 1.39 ± 1.01 mg/L, ranging from 0.20 to 3.90 mg/L. The water fluoride levels were stratified into four quartiles: Q1: ≤ 0.7 mg/L; Q2: 0.70 to 1.00 mg/L; Q3: 1.00 to 1.90 mg/L; Q4: > 1.90 mg/L. Similarly, the mean urinary fluoride among participants was 1.28 ± 1.30 mg/L, ranging from 0.01 to 5.54 mg/L. Urinary fluoride was also stratified into four quartiles: Q1: ≤ 0.15 mg/L; Q2: 0.15 to 0.41 mg/L; Q3: 0.41 to 2.28 mg/L; Q4: > 2.28 mg/L. Results from higher levels of water fluoride (i.e., Q2, Q3, Q4) were compared to those of lower water fluoride level (i.e., Q1 as reference).

Associations between fluoride exposure and thyroid hormones

When Q2 (0.70 to 1.00 mg/L) was compared with Q1 (≤ 0.7 mg/L) of water fluoride levels, there was no significant changes in all thyroid hormones investigated (i.e., TT3, FT3, TT4, FT4 and TSH). When all water fluoride levels of four quartiles ranging from 0.20 to 3.90 mg/L were included in the continuous analyses, there was no significant changes in thyroid hormone levels, except TSH, for every increase in 1 mg/L water fluoride levels. An increase in 1 mg/L water fluoride was associated with a statistically significant 0.127 µIU/mL increase in TSH (P = 0.028). This increase was within the normal range of TSH (i.e., 0.55 to 5.31 µIU/mL) in children 20 weeks to 18 years.[25]

When urinary fluoride was used to determine the association between fluoride exposure and thyroid hormones, there was no significant changes in all thyroid hormones (i.e., TT3, FT3, TT4, FT4 and TSH) when comparing between Q2 (0.15 to 0.41 mg/L) and Q1 (≤ 0.15 mg/L). In continuous analyses, every increase in 1 mg/L urinary fluoride, there was a significant 0.090 µg/dL decrease in TT4 (P = 0.017), and a significant 0.110 µIU/mL increase in TSH (P = 0.013). Similar to TSH, the small change in TT4 was within the normal range (i.e., 4.5 to 11.2 µg/dL).[26]

Associations between fluoride exposure and IQ scores

When comparing between Q2 (0.70 to 1.00 mg/L) and Q1 (≤ 0.7 mg/L) of water fluoride, or between Q2 (0.15 to 0.41 mg/L) and Q1 (≤ 0.15 mg/L) of urinary fluoride, there were no significant changes in IQ scores in total population, in boys or in girls.

When all water fluoride levels of four quartiles ranging from 0.20 to 3.90 mg/L were included in the continuous analyses, a statistically significant decrease of IQ scores was observed in total population (by 1.6 points), in boys (by 1.4 points) or in girls (by 1.6 points) for every increase in 1 mg/L water fluoride level. Similarly, an increase in 1 mg/L urinary fluoride was associated with a significant decrease of IQ scores was observed in total population (by 1.2 points), in boys (by 1.0 points) or in girls (by 1.64 points). The changes were relatively small and within the deviation of mean IQ of total population (i.e., 106.74 ± 11.82).

Associations between thyroid hormones and IQ scores

In continuous analyses including all concentrations of TT3 (0.052 to 1.97 ng/mL), FT3 (1.58 to 4.46 pg/mL), TT4 (3.90 to 10.92 µg/dL), FT4 (0.83 to 1.58 ng/dL) and TSH (0.34 to 10.97 µIU/mL), there was no significant association between any thyroid hormone and IQ score.

In summary, the study by Wang et al.[16] found no effect of water fluoride levels similar to CWF (i.e., 0.7 to 1.0 mg/L) on IQ scores in children aged 7 to 13 years. When all water fluoride levels (0.20 to 3.90 mg/L) were included in the analyses, there was approximately a 1.6 point decrease in IQ scores for every 1 mg/L increase in water fluoride. Similar observations were seen for urinary fluoride. The associations between fluoride exposure and thyroid hormones, and between thyroid hormones and IQs scores were insignificant.

3) The study by Riddell et al.[18] examined the association between fluoride exposure and ADHD in Canadian youth aged 6 to 17 years.

   Fluoride measurements

   Mean water fluoride concentrations was 0.49 ± 0.22 mg/L in fluoridated areas and 0.04 ± 0.06 mg/L in non-fluoridated areas. Mean urinary fluoride concentrations was 0.82 ± 0.54 mg/L in fluoridated areas and 0.46 ± 0.32 mg/L in non-fluoridated areas.

   The mean fluoride concentrations of tap water were 0.22 ± 0.24 mg/L and 0.29 ± 0.28 mg/L in the areas where children were diagnosed with ADHD and without ADHD, respectively. The mean urinary fluoride concentrations were 0.57 ± 0.32 mg/L and 0.62 ± 0.45 mg/L among children diagnosed with ADHD and without ADHD, respectively. No statistical comparisons were provided.

Assessment of ADHD and SDQ H/I subscale scores

Among total participants (N = 1,877), 7.3% (n = 137) were diagnosed with ADHD. The mean SDQ H/I subscale scores of children with ADHD diagnosis and children without ADHD diagnosis were 6.74 ± 2.5 and 2.51 ± 2.4, respectively.

Association between fluoride exposure and ADHD diagnosis

The study found no significant association between urinary fluoride and ADHD diagnosis. For every 1 mg/L increase of water fluoride, there was a 6.1 times higher odds of ADHD diagnosis, with a wide 95% confidence interval (CI) of 1.60 to 22.8. Interaction between age and water fluoride levels was not significant.

When CWF status was included in the analyses, CWF was associated with 1.2 times (95% CI 1.03 to 1.42) higher odds of ADHD diagnosis compared with non-CWF. The association between CWF and ADHD diagnosis was significant at the 75th percentile of age (i.e., 14 years old), but not at the 25th percentile of age (i.e., 9 years old).

Association between fluoride exposure and SDQ H/I subscale scores

The study found no significant association between urinary fluoride and SDQ H/I subscale scores. Every 1 mg/L increase of water fluoride was associated with a significant 0.31 points (95% CI 0.04 to 0.58) increase in SDQ H/I subscale score. When analyses based on CWF status, CWF was associated with 0.11 points (95% CI 0.02 to 0.20) increase in SDQ H/I subscale score compared to non-CWF. The association between water fluoride levels and SDQ H/I subscale scores, or between CWF status and SDQ H/I subscale scores was significant at the 75th percentile of age (i.e., 14 years old), but not at the 25th percentile of age (i.e., 9 years old).

In summary, the study by Riddell et al.[18] found no significant association between urinary fluoride and ADHD diagnosis, or between urinary fluoride and SDQ H/I subscale score. Higher water fluoride levels and CWF were positively associated with ADHD diagnosis and SDQ H/I subscale score.

Limitations

All three included studies had limitations in the internal validity due to biases in participant selection, classification of exposure, outcome assessment and statistical analyses as presented in the critical appraisal section. The insufficient adjustment of confounding factors limits the interpretation of the results, which precluded the establishment of causal relationships.

In the study by Till et al.,[17] the breastfed group had significant higher in FSIQ (by about 3 points) and VIQ (by out 5 to 7 points) compared to those who were formula-fed in both fluoridated and non-fluoridated areas. This suggests that children receiving breastfeeding might associate with higher IQ than those receiving formula-feeding, irrespective of fluoridation status. Maternal characteristics in this study showed that significantly lower proportion of mothers in the formula-fed group were married or common-law at the time of testing compared to the breastfed group irrespective to fluoridation status. Two important confounders were not adjusted in the analyses were marital status and mothers' IQ; and it has been shown that children's cognitive development would be at high risk when living with unmarried or lower IQ mothers.[27,28] The authors acknowledged that breastfed infants received low fluoride intake (less than 0.01 mg/L) even in CWF areas, and yet they found a decrease of 6.2 points in PIQ among breastfed infant for every 0.5 mg/L increase in water fluoride levels. This suggests that something other than water fluoride may affect children's IQ, assuming the analyses were correct and all important confounders were controlled. The non-validated formula used to estimate daily fluoride intake in the formula fed group over a course of one year had several limitations. First, the formula-feeding group was classified as infants who were never breastfed or partially breastfeeding within the first 6 months, and yet the daily fluoride intake was estimated based on 12 month feeding periods. Second, daily fluoride intake from weaning to the time of IQ assessment (i.e., 3 to 4 years) was not taken into consideration and adjusted in the analyses. Third, the authors did not adjust for fluoride contents in different formulas and assumed that fluoride intake was totally come from tap water. Fourth, there was a flaw in the assumption that mothers who lived fluoridated areas and drink tap water would use tap water to reconstitute the formula. The authors acknowledged that misclassification might occur due to unclear questionnaire, leading to recall or response bias. The changes in IQ scores in this study[17] was remarkably high compared to the previous study[15] from the same group of researchers using the same cohort of participants. This study[17] found a drop in 9.3 points and 6.2 PIQ points in formula-fed group and breastfed group, respectively, for every 0.5 mg/L increase in water fluoride level, or 18.6 points and 12.4 points for a 1 mg/L water fluoride increase, respectively. The study by Green et al. found a drop of 13.8 PIQ points in total population for every 1 mg/L water fluoride increase with wide 95% CI of -18.82 to -7.28.[15] This was an unprecedented observation for such large drop in IQ associated with water fluoride level in Canada.

The study by Wang et al.[16] appeared to use a more robust statistical analytic approach (i.e., adjustment for multiplicity) and found no significant differences between fluoride exposure and thyroid hormones, or between fluoride exposure and IQ scores when comparing fluoride levels that were similar to the CWF fluoride levels in Canada (i.e., 0.7 to 1.0 mg/L) to lower fluoride levels (i.e., < 0.7 mg/L). After considering all fluoride levels (i.e., from 0.2 to 3.9 mg/L) in the analyses, there was a decrease of 1.6 points in IQ for every 1 mg/L water fluoride. Although the association was significant, the change was small and may not be clinically relevant as the mean IQ of the total population was 106.74, with standard deviation of 11.82. The findings in this study were not applicable to the Canadian context and had limited generalizability to the Canadian population as the study was conducted in China, where socioeconomics and healthcare system are different than those in Canada.

In the study by Riddell et al.,[18] the authors found no significant association between urinary fluoride and ADHD diagnosis, or between urinary fluoride and SDQ H/I subscale score. However, higher fluoride levels in tap water and CWF were positively associated with ADHD diagnosis and SDQ H/I subscale score. The authors did provide explanations for such discrepancies, like the presence of fluoride from other sources such as foods, tea drinking, oral hygiene products, or swallowing toothpaste prior to urine sampling might affect urinary fluoride levels. However, all sources of fluoride exposure were not considered and controlled in the analyses. The authors acknowledged that tap water fluoride was measured in Cycle 3 only, thus reducing sample size for the analyses using fluoride in tap water as predictor. This may explain the lack of precision representing by wide confidence interval when examining for the association of between fluoride levels in tap water and ADHD diagnosis (OR = 6.10; 95% CI 1.60 to 22.80). Although the study found a 0.31 point SDQ H/I subscale score increase for every 1 mg/L water fluoride, and 0.11 points SDQ H/I subscale score increase for CWF versus non-CWF, these changes in scores were small and within the deviation of the means of SDQ H/I subscale scores of children with or without ADHD diagnosis. They were statistically significant but may not be clinically relevant.

Conclusions and Implications for Decision or Policy Making

This review included one prospective cohort study[17] and two cross-sectional studies[16,18] examining the effect of fluoride exposure on IQ[16,17] and ADHD diagnosis[18] in children. These studies are of low quality due to the multiple limitations (e.g., insufficient control of confounding factors, potential misclassification of exposure, and inappropriate study design).

The prospective cohort study by Till et al.[17] conducted in Canada examined fluoride exposure (determined by fluoridation status and fluoride intake from formula) over the first six months of feeding and IQ in children aged 3 to 4 years. The authors concluded that fluoride exposure during the first six months of infancy was associated with decrease non-verbal intelligence in children. The authors divided all regression coefficients by 2 and found that an increase of 0.5 mg/L of tap water fluoride levels was associated with 9.3 points and 6.2 PIQ points decrease in formula-fed group and breastfed group, respectively. The effect was significant and the changes in scores were quite large if they were converted back to per 1 mg/L fluoride levels. This was an unprecedented observation that exposure to fluoride at a non-endemic area, particularly at the Canadian water fluoride levels (optimum 0.7 mg/L) would result in a large drop in PIQ in children. The results also did not prove or disprove the hypothesis that fluoride intake from formula from reconstitution using fluoridated tap water reduces IQ, as the reduction in PIQ was found in both formula-fed and breastfed groups. The authors referred to the literature that breastmilk has extremely low concentrations of fluoride (0.005 to 0.01 mg/L) due to limited transfer of fluoride from plasma into breastmilk, and yet they found significant association between fluoride levels and PIQ reduction in breastfed group. Fluoride intake from breastmilk was not determined and no analysis on the association between fluoride intake from breastmilk and children's IQ was conducted as a control.

The cross-sectional study by Wang et al.[16] examined the association between fluoride exposure (water fluoride levels from 0.2 to 3.9 mg/L in the endemic and non-endemic areas in China) and IQ in children aged 7 to 13 years in relation to thyroid hormones. At water fluoride levels of 0.7 to 1.0 mg/L, the study found no significant difference in IQ scores or thyroid hormone levels compared to water fluoride levels of less than 0.7 mg/L. A regression analysis including all water fluoride levels showed a slight but significant decrease in IQ scores (by 1.6 points) for every 1 mg/L water fluoride. Although this study performed suitable statistical analyses, there are other study limitations that remain and impact the interpretation of findings (e.g., insufficient control for confounding factors).

The study by Riddell et al.,[18] conducted in Canada examined the association between fluoride exposure (determined by urinary fluoride, city fluoridation status and tap water fluoride levels) and ADHD in children aged 6 to 17 years. The authors concluded that children exposure to higher fluoride levels in tap water was associated with an increased risk of ADHD diagnosis in children, particularly in those of 14 years and older. However, the results showed no significant association between urinary fluoride and ADHD diagnosis, or between urinary fluoride and SDQ H/I subscale score. Water fluoride levels and CWF status were positively associated with ADHD diagnosis and SDQ H/I subscale score. The results were inconsistent that the interaction between water fluoride and age was not significant, whereas a significant interaction was found between CWF status and age. Although the association of water fluoride levels or CWF status with SDQ H/I subscale score was statistically significant, the changes in scores was rather small. Similar to the other two included studies,[16,17] this study[18] also had multiple limitations that may affect the interpretation of findings.

Considering the limitations and high risk of bias of the included studies, it is difficult to interpret their findings and generalize them the Canadian context. These correlation studies cannot produce valid interpretations of causality.

The recent CADTH HTA report[12] and the Rapid Response report[14] identified four studies relevant to the Canadian context that examined fluoride exposure on human IQ and cognitive function.[15,29-31]

The prospective cohort study by Broadbent et al. (2015)[29] was conducted with a cohort of children in New Zealand, who were followed for 38 years. The IQ was assessed repeatedly between 7 and 13 years and at age 38 years. The study found no statistically significant differences in IQ scores between residents in areas with CWF (0.7 mg/L to 1.0 mg/L) and those in areas without CWF (0.0 mg/L to 0.3 mg/L), after adjustment for confounding variables such as sex, socioeconomic status, low birth weight and breastfeeding. The authors concluded that it is unlikely that exposure to CWF at fluoride levels of 0.7 mg/L to 1.0 mg/L is neurotoxic and affects neurological development.

The ecological study by Aggeborn and Öhman (2017)[30] from Sweden examined the effect of lifetime fluoride exposure to the naturally occurring fluoride in drinking water (< 1.5 mg/L) on cognitive and non-cognitive ability in participants up to age 18 years, and math test scores in ninth grade students. It was found that water fluoride levels in Swedish drinking water had no effects on cognitive ability, non-cognitive ability, and math test scores, after adjusting for parent's education, parent's income, father's cognitive and non-cognitive ability, parent immigrant, and cohort mean education (at birth, at school start, and at 16 years age).

The cross-sectional study by Barberio et al. (2017)[31] examined the relationship between fluoride exposure and parental- or self-reported diagnosis of a learning disability among a population-based sample of Canadian children aged 3 to 12 years. It was reported that no significant association was observed between fluoride exposure and self-reported learning disability, self-reported diagnosis of ADHD, or self-reported diagnosis of attention deficit disorder.

The prospective cohort study by Green et al. (2019)[15] was included in the recent rapid response review report of CADTH.[14]This study examined the association between fluoride exposure of mothers during pregnancy and subsequent children's IQ scores at age 3 to 4 years. It found no significant association between maternal urinary fluoride and FSIQ in total sample of boys and girls. Only when splitting the analysis by sex, there was a significant, but rather small, reduction of 4.49 FSIQ score in boys for every 1 mg/L maternal urinary fluoride. In contrast, there was a non-significant increase in IQ scores in girls associated with increase maternal fluoride exposure.

Collective evidence from the recent CADTH reports[12,14] and the current review indicates there is insufficient evidence to conclusively conclude that fluoride exposure at the Canadian water fluoride levels (optimum at 0.7 mg/L) affects neurological development in children and adolescents in Canada.

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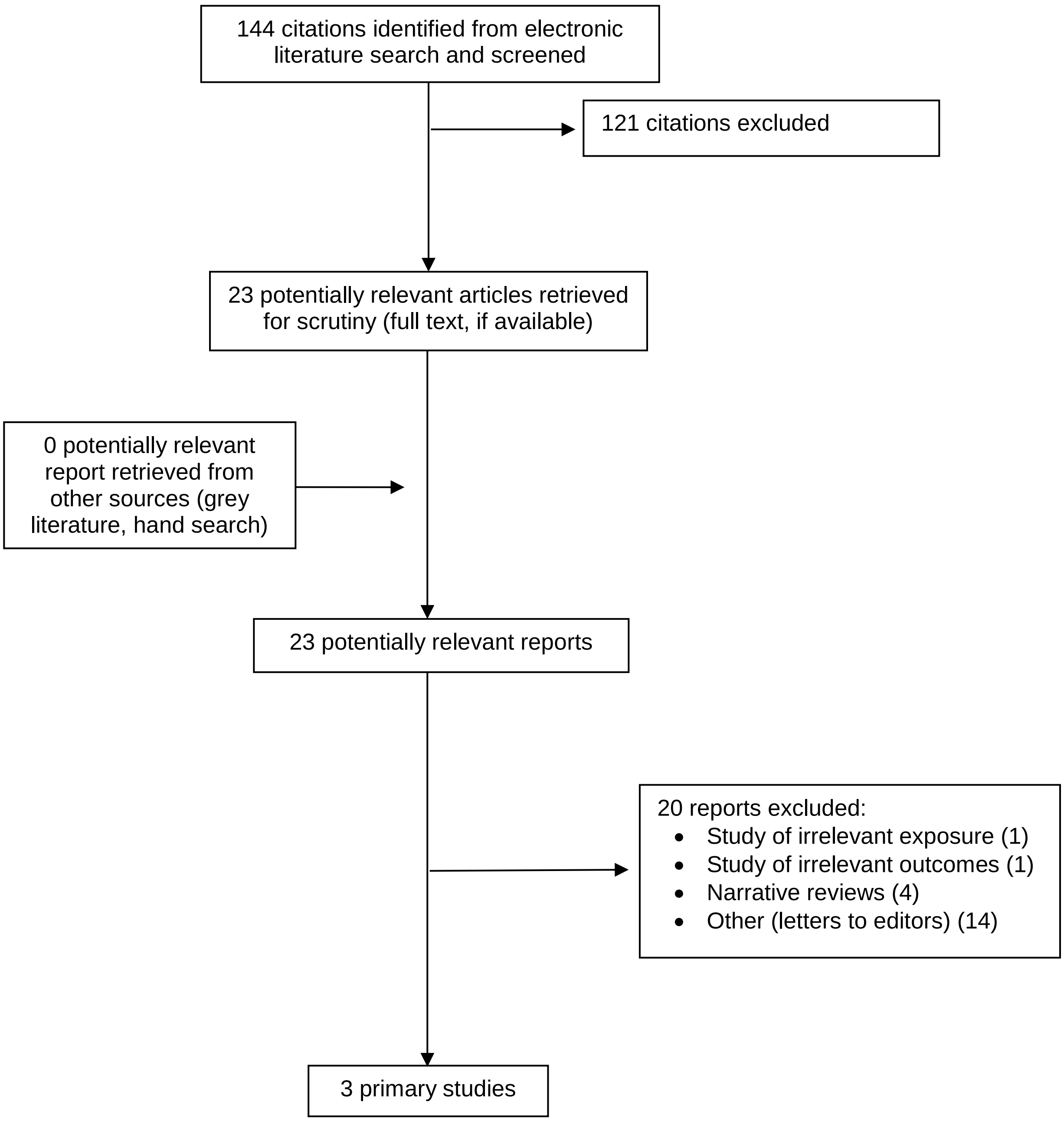
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Primary Studies

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Outcomes and Follow-up
Till et al., 2020[17] Canada Funding: The National Institute of Environmental Health Science	Prospective cohort study using data between 2008 to 2011 from the Maternal-Infant Research on Environmental Chemical (MIREC) program Mothers of children between 30 to 48 months completed infant-feeding questionnaire. Those who breastfed ≥ 6 months were put in the breastfeeding group; those who reported introducing formula within the first 6 months (never breastfed or partial breastfeeding) were put in the formula feeding group. Infant fluoride exposure was determined using mother's postal code that linked to a water treatment plan with known water fluoride levels over the first 6 months of child life. Fluoride intake from formula was estimated for one	Of 601 mother-child pairs who completed neurodevelopmental testing, 591 (99%) pairs completed the infant feeding questionnaire and IQ testing. 398 (67.3%) mother-child pairs who reported drinking tap water, had water fluoride data and complete covariate data were selected for analyses (breast-fed, n = 200; formula-fed, n = 189). <u>Mothers</u>: Mean age: 32 years; NS between fluoridation status or feeding status. Education: Mothers in the breast-fed group were more educated than those in the formula-fed group. Marital status: Significant higher proportion of mothers in the breast-fed group were married or common-law compared to those in the formula-group. HOME total score: significant higher score in the breast-fed group compared to the formula-group	CWF (n = 151) – Breast-fed (n = 83 – Formula-fed (n = 68) <u>Exposure variables</u>: Water fluoride levels in breast-fed group (mg/L) – Fluoridated: 0.58 (0.08) – Non-Fluoridated: 0.13 (0.06); P < 0.05 Water fluoride levels in formula-fed group (mg/L) – Fluoridated: 0.59 (0.07) – Non-Fluoridated: 0.13 (0.05); P < 0.05 Infant fluoride intake in breast-fed group (mg F/day) – Fluoridated: 0.12 (0.07) – Non-Fluoridated: 0.02 (0.02); P < 0.05 Infant fluoride intake in formula-fed group (mg F/day) – Fluoridated: 0.34 (0.12) – Non-Fluoridated: 0.08 (0.04); P < 0.05 MUF concentration in breast-fed group (mg/L) – Fluoridated: 0.70 (0.39) – Non-Fluoridated: 0.42 (0.28); P < 0.05 MUF concentration in formula-fed group (mg/L) – Fluoridated: 0.64 (0.37) – Non-Fluoridated: 0.38 (0.27); P < 0.05	Non-CWF (n = 247) – Breast-fed (n = 117 – Formula-fed (n = 130)	– FSIQ (a measure of global intellectual functioning) – VIQ (a measure of verbal reasoning) – PIQ (a measure of non-verbal reasoning and visual-motor coordination skill) Children at 3 to 4 years old were assessed for intellectual abilities using the Wechsler Preschool and Primary Scale of Intelligence-III using the US population-based normative data (mean = 100, SD = 15)

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Outcomes and Follow-up
	year using a non-validated method. Fetal fluoride exposure was estimated from maternal urinary fluoride adjusted for specific gravity. Linear regression was used to assess differences in child IQ by water fluoride concentration. First model looked at the association between IQ scores and water fluoride concentration by feeding status. Second model estimated association between fluoride intake from formula and child IQ. Covariates (i.e., child's sex and age at testing, maternal education, maternal race, smoke in the home, and quality of child's home environment)	Income: NS between feeding status Employed: NS between feeding status Smoked in trimester 1: NS between feeding status Number of months exclusively breast feeding: – Breast-fed: 7.5 months – Formula-fed: 2.5 months <u>Children</u>: Age at IQ testing: 3.4 years; NS between feeding status % female: 51%; NS between feeding status Second-hand smoke: NS between feeding status Birth weight: NS between feeding status Gestational age; NS between feeding status FSIQ in breast-fed group – Fluoridated: 109.9 (12.4) – Non-Fluoridated: 108.9 (13.6); NS FSIQ in formula-fed group – Fluoridated: 106.1 (15.8)			

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Outcomes and Follow-up
		– Non-Fluoridated: 106.8 (13.5); NS VIQ in breast-fed group – Fluoridated: 115.1 (11.3) – Non-Fluoridated: 110.4 (12.4); P < 0.05 VIQ in formula-fed group – Fluoridated: 110.9 (14.9) – Non-Fluoridated: 107.1 (13.3); NS PIQ in breast-fed group – Fluoridated: 102.0 (15.2) – Non-Fluoridated: 105.6 (15.8); NS PIQ in formula-fed group – Fluoridated: 99.7 (15.1) – Non-Fluoridated: 105.6 (13.4); P < 0.05			
Wang et al., 2020[16] China Funding: Not reported	Cross-sectional study conducted in 2015 in the rural areas of Tianjin City, China. The upper limit of drinking water fluoride was 1 mg/L (i.e., normal fluoride: ≤ 1 mg/L; high fluoride: > 1 mg/L). The study participants were selected using a stratified and multistage	Children 7 to 13 years old (N = 571) Age (SD): 9.8 (1.05) years Gender Boys: 51.1% Girls: 48.9% Height (SD): 141.86 (8.96) cm Weight (SD): 36.28 (10.73) kg BMI (SD): 17.74 (3.69) kg/m^2	Exposure to higher levels of water fluoride (i.e., 0.70 to 1.00 mg/L; 1.00 to 1.90 mg/L; > 1.90 mg/L) Water fluoride concentration ranged from 0.2 mg/L to 3.9 mg/L, mean value (SD) was 1.39 (1.01) mg/L.	Exposure to lower levels of water fluoride (i.e., ≤ 0.7 mg/L)	IQ scores A combined Raven's Test for Rural China (CRT-RC2) was used to evaluate the IQ in each child. The test assessed a range of intelligence functions without depending on language skills. The test had 72 questions in six sets of 12. The examiners were blinded.

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Outcomes and Follow-up
	random sampling approach. Water samples were collected randomly from the public water supplies in each village, and urine samples were collected in the early morning before breakfast. Fluoride contents in the water and urine were measured using fluoride ion selective electrode. Thyroid hormones (TT3, TT4, FT3, FT4 and TSH) were measured using chemiluminescent microparticle immunoassay. Multivariable linear regressions were used to estimate the changes in THs and IQ scores for every 1 mg/L increase in water fluoride and urinary fluoride concentrations. Water fluoride was divided into four quartiles: ≤ 0.7 mg/L; 0.70 to 1.00 mg/L; 1.00 to 1.90 mg/L; > 1.90 mg/L Covariates (i.e., age, gender, BMI,	Low birth weight: 4.6% Household income (RMB/year) <10,000: 7.9% 10,000 – 30,000: 39.6% >30,000: 45.9% Paternal education Middle school and below: 81.4% High school: 13.1% Junior college and above: 3.5% Maternal education Middle school and below: 83.9% High school: 10.3% Junior college and above: 3.3% IQ scores (SD): 106.74 (11.82) IQ levels ≥130: 3.5% 120 – 129: 9.3% 110 – 119: 25.4% 90 – 109: 54.3% 70 – 89: 7.5% Urinary fluoride ranged from 0.001 mg/L to 5.54 mg/L, mean (SD) was 1.28 (1.3) mg/L. Mean THs values TT3: 1.33 ng/mL TT4: 6.8 µg/dL FT3: 3.28 pg/mL FT4: 1.53 ng/dL TSH: 2.28 uIU/mL			

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Outcomes and Follow-up
	paternal education level, maternal education level, household income, and low birth weight) Benjamin-Hochberg false discovery rate procedure was applied to address multiple testing corrections. The significance was determined by a false discovery rate of Q = 0.05 and m = 5 tests. $P < 0.05$ was considered as statistical significance.				
Riddell et al., 2019[18] Canada Funding: Minor Research Grant rom the Faculty of Health at York University	Cross-sectional study using data from the Canadian Health Measures Survey (CHMS); Cycle 2 (2009 to 2011) and Cycle 3 (2012 to 2013) Urinary fluoride was measured using an Orion pH meter with a fluoride ion electrode on urine spot samples. Limit of detection was 20 µg/L for cycle 2 and 10 µg/L for cycle 3). The concentrations were adjusted for specific gravity (UF_{SG}).	Children 6 to 17 years old Three samples used in the analyses, representing three types of fluoride exposure: Sample 1 (N = 1,877 from cycle 2 and 3) having urinary fluoride measurement Sample 2 (N = 1,722 from cycle 2 and 3) having known city fluoride status (n = 932 in fluoridated area; n = 790 in non-fluoridated area) Sample 3 (N = 710 from cycle 3) with tap fluoride measurement who drink tap water	Exposure to higher levels of fluoride determined by UF_{SG}, CWF status, and tap water fluoride level Fluoride measures: – UF_{SG} at sites with CWF: 0.82 (0.54) mg/L – UF_{SG} at sites without CWF: 0.46 (0.32) mg/L – Water fluoride level at site with CWF: 0.49 (0.22) – Water fluoride level at site without CWF: 0.05 (0.06) Fluoride measures between children with and without ADHD diagnosis: – Tap water fluoride concentrations (mg/L): ADHD: 0.29 (0.28) No ADHD: 0.22 (0.24)	Exposure to lower levels of fluoride determined by UF_{SG}, CWF status, and tap water fluoride level	Primary outcomes: – SDQ hyperactive/ inattention score – ADHD diagnosis The SDQ has 25 items with a 3-point response scale (0 = not true; 1 = somewhat true; 2 = certainly true). These items are grouped into five subscales: emotional problems, conduct problems, hyperactivity-inattention, peer problem, and prosocial behaviour. Scores in each subscale

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Outcomes and Follow-up
	Fluoride levels in tap water were measured by ion exchange chromatography with a limit of detection of 0.006 mg/L. Logistic regression models were used to examine the associations between each fluoride exposure (i.e., UF_{SG}, CWF status, tap water fluoride level) and ADHD with the same set of covariates. Linear regression models were used to examine the associations between each fluoride exposure (i.e., UF_{SG}, CWF status, tap water fluoride level) and the SDQ hyperactivity /inattention subscale score. Covariates (i.e., sex, age, ethnicity, BMI, level of education obtained by either parent, total household income, exposure to cigarette smoke at home, and level of blood lead) P < 0.05 was considered as	Child sex: – Male: 50.8% to 52.7% – Female: 47.3% to 49.2% Mean child age at interview: 11.3 (3.4) years Parental education: – University or higher: 47.0% to 56.6% – Highschool or college: 43.4% to 53.0% Smoking in the home: – Yes: 7.7% to 11.5% – No: 88.5% to 92.4% Mean household income: $91,700 to $104,000 BMI: 19.6 to 19.8 kg/m^2 Blood lead: 0.83 µg/dL Period lived in residence: – < 3 years: 0 to 21.1% – ≥ 3 years: 78.9 to 100% Fluoride measures: – UF_{SG}: 0.61 to 0.64 mg/L – Water fluoride: 0.23 to 0.26 mg/L Site with added fluoride:	– UF_{SG} (mg/L) ADHD: 0.57 (0.32) No ADHD: 0.62 (0.45) SDQ H/I subscale score: – ADHD: 6.74 (2.5) – No ADHD: 2.51 (2.4)		range from 0 to 10. ADHD was diagnosed by doctors. Questions for ADHD diagnosis differed between cycle 2 and cycle 3. In cycle 2: *“Do you have a learning disability”*, if Yes, then specify type of learning disability: 1) ADD; 2) ADHD; 3) Dyslexia; 4) other. In cycle 3: Children were asked whether they received physician-diagnosed ADHD, and if so, which subtype. Parents or guardians provided information for children age 6 to 11 years. Children 12 to 17 years completed the questionnaire and answered the question.

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Outcomes and Follow-up
	statistical significance.	– Yes: 50.9% to 53.7% – No: 46.3% to 48.1% Diagnosis of ADHD: 5.5% to 7.3%; n = 137 in the analyses. Without ADHD, n= 1,740. SDQ H/I subscale score: 2.6 to 2.9			

ADD = attention deficit disorder; ADHD = attention deficit hyperactive disorder; BMI = body mass index; CWF = community water fluoridation; FT3 = free triiodothyronine; FT4 = free thyronine; SDQ H/I = Strengths and Difficulties Questionnaire; ppm = part per million; TSH = thyroid-stimulating hormone; TT3 = total triiodothyronine; TT4 = total thyronine; UF_{SG} = urinary fluoride adjusted for specific gravity.

Appendix 3: Critical Appraisal of Included Publications

Table 3: Quality Assessment of Studies Reporting Correlations and Associations

NICE Checklist[19]	Till et al., 2020[17]	
Question	**Answer**	**Comment**
SECTION 1: POPULATION		
1.1 Is the source population or source area well described?	Yes	The Maternal-Infant Research on Environment Chemicals (MIREC) recruited pregnant persons within the first 14 weeks of pregnancy from 10 cities in Canada. A subset of 610 mother-child pairs in the MIREC study were recruited from 6 of 10 cities: Vancouver, Montreal, Kingston, Toronto, Hamilton, and Halifax. 601 completed all testing. Children aged 3 to 4 years.
1.2 Is the eligible population or area representative of the source population or area?	Probably no	The recruitment of individuals, clusters or areas was not defined. It was unclear how 6 of 10 cities were chosen.
1.3 Do the selected participants or areas represent the eligible population or area?	Probably no	The method of selection of participants from the eligible population was not described. There was no report on the percentage of selected individuals or clusters who agreed to participate. Risk of selection bias.
SECTION 2: METHOD OF ALLOCATION TO INTERVENTION (OR COMPARISON)		
2.1 Selection of exposure (and comparison) group. How was selection bias minimized?	Acceptable	Infant fluoride exposure was determined using mother's postal code that linked to a water treatment plan with known water fluoride levels over the first 6 months of child life. Fluoride intake from formula was estimated for one year using a non-validated method. Fetal fluoride exposure was estimated from maternal urinary fluoride adjusted for specific gravity. Mother-child pairs were sorted out based on feeding status (i.e., breast-fed or formula fed) through questionnaire, and by fluoridated areas (i.e., fluoridation or non-fluoridation). There was some attempt to minimize selection bias.
2.2 Was the selection of explanatory variables based on sound theoretical basis?	Probably no	Evidence for the hypothesis that infant fluoride exposure was associated with lower IQ in children was drawn from studies conducted in countries not applicable to the Canadian context (e.g., use of fluoridated salts, or water fluoride levels many folds higher than the current recommended level in Canada)
2.3 Was the contamination acceptable low?	No	Fluoride exposure did not specifically come from CWF; it could be from other sources such as foods or swallowing toothpaste after toothbrushing.
2.4 How well were likely confounding factors identified and controlled?	Partially	Covariates (i.e., child's sex and age at testing, maternal education, maternal race, smoke in the home, and quality of child's home environment) were adjusted in the regression analysis. Potentially missing covariates included socioeconomic status, first-born, low birth weight, paternal education, maternal and paternal IQ, alcohol consumption, nutritional contents in breast milk and formula, marital status, migration, and children fluoride exposure and other

NICE Checklist[19]	Till et al., 2020[17]	
		chemical exposure between the period of feeding and intelligence assessment.
2.5 Is the setting applicable to the Canadian context?	Yes	The study was conducted in Canada
SECTION 3: OUTCOMES		
3.1 Were the outcome measures and procedures reliable?	Partially	Mothers of children between 30 to 48 months completed a non-validated infant-feeding questionnaire. Those who breastfed ≥ 6 months were put in the breastfeeding group; those who reported introducing formula within the first 6 months (never breastfed or partial breastfeeding) were put in the formula feeding group. Infant fluoride exposure was determined using mother's postal code that linked to a water treatment plan with known water fluoride levels over the first 6 months of child life. Fluoride intake from formula was estimated for one year using a non-validated method. Fetal fluoride exposure was estimated from maternal urinary fluoride adjusted for specific gravity. Children's IQ was assessed using the Wechsler Preschool and Primary Scale of Intelligence, third Edition. The knowledge of the classification of exposure and feeding status might have affected the scoring of children's IQ.
3.2 Were the outcome measurements complete?	No	Results from all recruited participants were not reported. Over one third were excluded due to missing data. Unclear if missing IQ data from excluded children could affect the findings.
3.3 Were all the important outcomes assessed?	Yes	Full Scale IQ, verbal IQ and performance IQ were measured.
3.4 Was there a similar follow-up time in exposure and comparison groups?	Probably No	Children's intellectual abilities were assessed between 3 and 4 years. However, it was unclear if all included children had lived in the same areas since birth. Also, it was unclear about the period of fluoride exposure of mothers. Some mothers might have a lifetime exposure, while others might just have exposure during pregnancy.
3.5 Was follow-up time meaningful?	No	The WPPSI-III provides different sets of subtests for the 2 years 6 months to 3 years 11 months age band and the 4years to 7 years 7 months age band. Intelligence tests were performed between the age of 3 and 4 years, the exact age of the children at the time point of the test has not been considered in the statistical analysis. IQ of children changed strongly between 3 and 4 years. There was a gap between first year of feeding and intelligence assessment (children aged 3 to 4 years) that the fluoride exposure and fluoride intake were not taken into account.
SECTION 4: ANALYSES		
4.1 Was the study sufficiently powered to detect an intervention effect (if one exists)?	No	The study did not report if it performed any sample calculation to obtain sufficient power to detect an intervention effect. The sample size was relatively small.

NICE Checklist[19]	Till et al., 2020[17]	
		Among formula-fed group, only 68 were in the fluoridated areas compared with 130 in the non-fluoridated areas.
4.2 Were multiple explanatory variables considered in the analyses?	Yes	Two measures of fluoride exposure (water fluoride concentration and infant fluoride intake from formula) were used in the analyses for the association between fluoride exposure and children's IQ.
4.3 Were the analytical methods appropriate?	Probably no	Linear regression was used to assess differences in child IQ by water fluoride concentration. First model looked at the association between IQ scores and water fluoride concentration by feeding status. Second model estimated association between fluoride intake from formula and child IQ. The association of confounders with IQ were not presented separately for each confounder, and all the influential confounders were not identified and included in the multivariable analysis.
4.4 Was the precision of association given or calculable? Is association meaningful?	Probably no	Test statistics and associated *P* values reported for all analyses. R-squared values for linear regression were not reported. Unclear if association was meaningful. The study did not conduct multiple testing adjustment to account for multiplicity. With the P value of 0.05, there was a high likelihood of detecting false positive finding with multiple statistical tests. The study assumed that association between water fluoride levels and IQ in children was linear, so the regression coefficients were divided by 2 to predict the IQ difference per 0.5 mg/L. It is unclear whether that assumption has been validated.
SECTION 5: SUMMARY		
5.1 Are the study results internally valid (i.e., unbiased)?	No	High risk of bias due to selection of participants, classification of intervention, confounding, missing data, and measurement of outcomes
5.2 Are the findings generalizable to the source population (i.e., externally valid)?	Probably not	Although the study was conducted in Canada, there was a risk of selection bias of the participants into the sample, and small sample size. The findings could not be generalizable to the entire Canadian population.

CWF = community water fluoridation; HOME = Home Observation for Measurement of the Environment; IQ = intelligence quotient

NICE Checklist	Wang et al., 2020[16]	
Question	**Answer**	**Comment**
SECTION 1: POPULATION		
1.1 Is the source population or source area well described?	Yes	Resident children, aged 7 to 13 years, were recruited from endemic and non-endemic fluorosis rural areas in Tianjin, China. The whole district was divided into high fluoride areas and normal fluoride areas according to the upper limit of 1 mg/L. None of the study sites was exposed to neurotoxins known affecting IQ such as arsenic, lead or mercury in drinking water. However, data were not shown.
1.2 Is the eligible population or area representative of the source population or area?	Yes	The study participants were selected using a stratified and multistage random sampling approach.

NICE Checklist	Wang et al., 2020[16]	
1.3 Do the selected participants or areas represent the eligible population or area?	Probably no	The method of selection of participants from the eligible population was well described. However, there was no report on the percentage of selected individuals or clusters who agreed to participate. Risk of selection bias.
SECTION 2: METHOD OF ALLOCATION TO INTERVENTION (OR COMPARISON)		
2.1 Selection of exposure (and comparison) group. How was selection bias minimized?	Acceptable	Fluoride exposure was assessed by fluoride content in the water and from children's urine. There was clear pre-defined level of fluoride exposure that was considered as low or high at start of the study with the upper limit of 1 mg/L. Water fluoride levels were divided into four quartiles: Q1 (≤0.7 mg/L), Q2 (0.70 to 1.0 mg/L), Q3 (1.00 to 1.90 mg/L), Q4 (>1.90 mg/L). Children who were not long-term residents of the area were excluded. However, definition of long-term was not provided. Other than that, no further attempt was reported to minimize selection bias.
2.2 Was the selection of explanatory variables based on sound theoretical basis?	Probably no	Evidence for the hypothesis that thyroid hormones might play a role in the association between fluoride exposure and children's intelligence was based on animal and human studies conducted with high levels of fluoride.
2.3 Was the contamination acceptable low?	No	Fluoride exposure did not specifically come from drinking water; it could be from other sources such as foods or swallowing toothpaste after toothbrushing.
2.4 How well were likely confounding factors identified and controlled?	Partially	Some confounding factors such as age, gender, BMI, paternal education level, maternal education level, household income, and low birth weight were adjusted in the regression analysis. Potential missing confounding factors were water improvement plants (whether fluoride, lead, or arsenic removed from drinking water), breastfeeding, other sources of fluoride (e.g., foods, oral hygiene products), parents' socioeconomic status and IQ, first-born, intake of iodine, and exposures to other chemicals, like lead, mercury, arsenic.
2.5 Is the setting applicable to the Canadian context?	No	The study was conducted in China
SECTION 3: OUTCOMES		
3.1 Were the outcome measures and procedures reliable?	Yes	Water samples were collected randomly from the public water supplies in each village, and urine samples were collected in the early morning before breakfast. Fluoride contents in the water and urine were measured using fluoride ion selective electrode. Thyroid hormones (TT3, TT4, FT3, FT4 and TSH) were measured using chemiluminescent microparticle immunoassay. A combined Raven's Test for Rural China (CRT-RC2) was used to evaluate the IQ in each child. The test assessed a range of intelligence functions without depending on language skills. The test had 72 questions in six sets of 12. The examiners were blinded.

NICE Checklist	Wang et al., 2020[16]	
3.2 Were the outcome measurements complete?	Probably yes	Outcome measurements appeared to be completed in all participants.
3.3 Were all the important outcomes assessed?	Yes	IQ was assessed using a combined Raven's Test for Rural China (CRT-RC2).
3.4 Was there a similar follow-up time in exposure and comparison groups?	Probably not	The characteristics including age were not separately reported for each group, and therefore, it was unclear if follow-up time was similar between groups.
3.5 Was follow-up time meaningful?	Probably not	It was unclear if they all children lived in the areas since birth. A combined Raven's Test for Rural China (CRT-RC2) was used to evaluate the IQ in each child aged between 7 and 13 years, but the exact age of the children at the time point of the test has not been considered in the statistical analysis.
SECTION 4: ANALYSES		
4.1 Was the study sufficiently powered to detect an intervention effect (if one exists)?	No	The study did not perform any sample calculation to obtain sufficient power to detect an intervention effect.
4.2 Were multiple explanatory variables considered in the analyses?	Probably yes	Two measures of fluoride exposure (water fluoride and urinary fluoride) were used in the analyses for the association between fluoride exposure and children's IQ. However, urinary fluoride was not adjusted by urine creatinine or specific gravity to account for dilution, as fluoride levels were measured in early morning spot urine samples instead of 24-hour urine collections.
4.3 Were the analytical methods appropriate?	Probably Yes	Multivariable linear regressions were used to estimate the changes in THs and IQs score for every 1 mg/L increase in water fluoride and urinary fluoride concentrations, with the adjustment of covariates.
4.4 Was the precision of association given or calculable? Is association meaningful?	Probably yes	Test statistics and associated *P* values reported for all analyses. R-squared values for linear regression were not reported. Unclear if association was meaningful. Benjamin-Hochberg false discovery rate procedure was applied to address multiple testing corrections. The significance was determined by a false discovery rate of Q = 0.05 and m = 5 tests.
SECTION 5: SUMMARY		
5.1 Are the study results internally valid (i.e., unbiased)?	No	High risk of bias due to selection of participants, classification of intervention, confounding, and measurement of outcomes
5.2 Are the findings generalizable to the source population (i.e., externally valid)?	No	The study was conducted in China. Fluoridation, healthcare and socioeconomics are different to the Canadian context.

CWF = community water fluoridation; HOME = Home Observation for Measurement of the Environment; IQ = intelligence quotient

NICE Checklist	Riddle et al., 2019[18]	
Question	**Answer**	**Comment**
SECTION 1: POPULATION		
1.1 Is the source population or source area well described?	Yes	Data were from the Canadian Health Measures Survey (CHMS); Cycle 2 (2009 to 2011) and Cycle 3 (2012 to 2013).

NICE Checklist	Riddle et al., 2019[18]	
1.2 Is the eligible population or area representative of the source population or area?	Probably yes	Three samples used in the analyses, representing three types of fluoride exposure: Sample 1 (N = 1,877 from cycle 2 and 3) having urinary fluoride measurement Sample 2 (N = 1,722 from cycle 2 and 3) having known city fluoride status (n = 932 in fluoridated area; n = 790 in non-fluoridated area) Sample 3 (N = 710 from cycle 3) with tap fluoride measurement who drink tap water
1.3 Do the selected participants or areas represent the eligible population or area?	Probably no	The method of selection of participants from the eligible population was not described. Risk of selection bias.
SECTION 2: METHOD OF ALLOCATION TO INTERVENTION (OR COMPARISON)		
2.1 Selection of exposure (and comparison) group. How was selection bias minimized?	Acceptable	Fluoride exposure assessed by urinary fluoride, city fluoridation status and levels of fluoride in tap water. However, other sources of fluoride exposure were not considered. No attempt was reported to minimize selection bias. Misclassification might occur due to changes in areas of residency.
2.2 Was the selection of explanatory variables based on sound theoretical basis?	Probably no	Evidence for the hypothesis that childhood fluoride exposure was associated with adverse behavioral outcomes in children was drawn from animal and human studies with high water fluoride levels.
2.3 Was the contamination acceptable low?	No	Fluoride exposure did not specifically come from CWF; it could be from other sources such as foods or oral hygiene products.
2.4 How well were likely confounding factors identified and controlled?	Partially	Some confounding factors such as sex, age, ethnicity, BMI, level of education obtained by either parent, total household income, exposure to cigarette smoke at home, and level of blood lead were adjusted in the regression analysis. Potential missing confounders included residency, other sources of fluoride, water improvement plans, breastfeeding, hereditary factor, other sources of fluoride, parental IQ and socioeconomic status, alcohol consumption, first-born, low birth weight, and exposure to other chemicals.
2.5 Is the setting applicable to the Canadian context?	Yes	The study was conducted in Canada
SECTION 3: OUTCOMES		
3.1 Were the outcome measures and procedures reliable?	Partially	Urinary fluoride was measured from urine spot sample, instead of 24-hour urine, using an Orion pH meter with a fluoride ion electrode on urine spot samples. Limit of detection was 20 µg/L for cycle 2 and 10 µg/L for cycle 3). The concentrations were adjusted for specific gravity (UF_{SG}). Fluoride levels in tap water were measured by ion exchange chromatography with a limit of detection of 0.006 mg/L. The SDQ has 25 items with a 3-point response scale (0 = not true; 1 = somewhat true; 2 = certainly true). These items are grouped into five subscales: emotional problems,

NICE Checklist	Riddle et al., 2019[18]	
		conduct problems, hyperactivity-inattention, peer problem, and prosocial behaviour. Scores in each subscale range from 0 to 10. ADHD was diagnosed by doctors. Questions for ADHD diagnosis differed between cycle 2 and cycle 3. In cycle 2: *"Do you have a learning disability"*, if Yes, then specify type of learning disability: 1) ADD; 2) ADHD; 3) Dyslexia; 4) other. In cycle 3: Children were asked whether they received physician-diagnosed ADHD, and if so, which subtype. Self-reported on ADHD diagnosis was likely subjected to reporting bias.
3.2 Were the outcome measurements complete?	Probably yes	The outcome measurements appear to be complete
3.3 Were all the important outcomes assessed?	Yes	Self-reported physician-diagnosed ADHD and hyperactive/inattention score on the Strengths and Difficulties questionnaire were assessed.
3.4 Was there a similar follow-up time in exposure and comparison groups?	Probably not	The study stated that children must have lived in the areas for three or more years, but did not show whether there was any difference in the residing time between exposure and comparison groups.
3.5 Was follow-up time meaningful?	Probably not	Outcomes were assessed at only one time point in population with wide age range (i.e., 6 and 17 years).
SECTION 4: ANALYSES		
4.1 Was the study sufficiently powered to detect an intervention effect (if one exists)?	No	The study did not perform any sample calculation to obtain sufficient power to detect an intervention effect.
4.2 Were multiple explanatory variables considered in the analyses?	Yes	Three measures of fluoride exposure (urinary fluoride adjusted for specific gravity, city fluoridation status and tap water fluoride level) were used in the analyses for the association between fluoride exposure and children's ADHD.
4.3 Were the analytical methods appropriate?	Probably Yes	Logistic regression models were used to examine the associations between each fluoride exposure (i.e., UF_{SG}, CWF status, tap water fluoride level) and ADHD with the same set of covariates. Linear regression models were used to examine the associations between each fluoride exposure (i.e., UF_{SG}, CWF status, tap water fluoride level) and the SDQ hyperactivity /inattention subscale score.
4.4 Was the precision of association given or calculable? Is association meaningful?	Probably yes	Test statistics and associated P values reported for all analyses. R-squared values for linear regression were not reported. Unclear if association was meaningful. $P < 0.05$ was considered as significant difference. However, adjustment for multiplicity due to multiple statistical testing was not performed, thus increasing the likelihood of detecting a false positive outcome.
SECTION 5: SUMMARY		

NICE Checklist	Riddle et al., 2019[18]	
5.1 Are the study results internally valid (i.e., unbiased)?	No	High risk of bias due to selection of participants, misclassification, improper control of confounding factors, missing data, and measurement of outcomes.
5.2 Are the findings generalizable to the source population (i.e., externally valid)?	Probably not	Although the study was conducted in Canada, there was a risk of selection bias of the participants into the sample. The findings could not be generalizable to the entire Canadian population.

CWF = community water fluoridation; HOME = Home Observation for Measurement of the Environment; IQ = intelligence quotient

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Findings of Included Primary Studies

Main Study Findings	Author's Conclusions
Till et al., 2020[17]	
Data of 398 mother-child pairs were entered into the analyses – City fluoridation status (Fluoridated, n = 151, 37.9%; non-fluoridated, n = 247, 62.1%) – Feeding status (Breastfed, n = 200, 50.3%; formula-fed, n = 198, 49.7%) IQ assessment FSIQ scores – mean [SD] – Breastfed (Fluoridated: 109.9 [12.4]; non-fluoridated: 109.9 [13.6]); NS – Formula-fed (Fluoridated: 106.1 [15.8]; non-fluoridated: 106.8 [13.5]); NS – There were no significant differences in FSIQ between fluoridated and non-fluoridated in both breastfed group and formula-fed group. – Comparing between breastfed and formula-fed, mean FSIQ scores of children in formula-fed group was significantly lower than those in breastfed group (P = 0.03) by about 3 points in both fluoridated and non-fluoridated areas. VIQ scores – mean [SD] – Breastfed (Fluoridated: 115.1 [11.3]; non-fluoridated: 110.4 [12.4]); P = 0.02; after adjustment for covariates – Formula-fed (Fluoridated: 110.9 [14.9]; non-fluoridated: 107.1 [13.3]); NS; after adjustment for covariates – Among breastfed group, children in the fluoridated areas had significantly higher VIQ scores by 5 points than those in the non-fluoridated areas. There was no significant difference in VIQ scored among formula-fed group who lived either in the fluoridated or non-fluoridated areas. – Comparing between breastfed and formula-fed, VIQ of children in formula-fed group was significantly lower than those in breastfed group (P = 0.00) by about 5 and 3 points in both fluoridated and non-fluoridated areas, respectively. PIQ scores – mean [SD] – Breastfed (Fluoridated: 102.0 [15.2]; non-fluoridated: 105.6 [15.8]); NS; after adjustment for covariates. – Formula-fed (Fluoridated: 99.7 [15.1]; non-fluoridated: 105.6 [13.4]); P < 0.001; after adjustment for covariates. – Among formula-fed group, children in the fluoridated areas had significantly lower PIQ scores by 6 points than those in the non-fluoridated areas. There was no significant difference in PIQ scored among breastfed group who lived either in the fluoridated or non-fluoridated areas. – Comparing between breastfed and formula-fed, there was no significant difference in PIQ irrespective to the city fluoridation status (P = 0.69). Exposure variables Water fluoride concentrations – mean [SD]; mg/L – Breastfed (Fluoridated: 0.58 (0.08); non-fluoridated: 0.13 [0.06]); p < 0.05 – Formula-fed (Fluoridated: 0.59 (0.07); non-fluoridated: 0.13 [0.05]); p < 0.05 Infant fluoride intake – mean [SD]; mg F/day – Breastfed (Fluoridated: 0.12 (0.07); non-fluoridated: 0.02 [0.02]); p < 0.05 – Formula-fed (Fluoridated: 0.34 (0.12); non-fluoridated: 0.08 [0.04]); p < 0.05 – Comparing between breastfed and formula-fed, infant fluoride intake was significantly lower in breastfed children in both fluoridated and non-fluoridated areas (P < 0.001). MUF concentrations – mean [SD]; mg/L	*"Exposure to increasing levels of fluoride in the tap water was associated with diminished non-verbal intellectual abilities; the effect was more pronounced among formula-fed children."*[17] (p1)

Main Study Findings	Author's Conclusions
– Breastfed (Fluoridated: 0.70 (0.39); non-fluoridated: 0.42 [0.28]); p < 0.05 – Formula-fed (Fluoridated: 0.64 (0.37); non-fluoridated: 0.38 [0.27]); p < 0.05 – Comparing between breastfed and formula-fed, there was no significant difference in MUF irrespective to the city fluoridation status (P = 0.07). Regression coefficient B (95% CI) for every increase in 0.5 mg/L water fluoride concentration or for every increase in 0.5 mg fluoride intake from formula per day. Association between water fluoridation status and IQ scores without adjusting for MUF. – Breastfed FSIQ: - 1.34 (- 5.04 to 2.38) PIQ: - 6.19 (- 10.45 to - 1.94); P < 0.05 VIQ: 3.06 (- 0.49 to 6.61) – Formula-fed FSIQ: - 4.40 (- 8.34 to - 0.46); P < 0.05 PIQ: - 9.26 (- 13.77 to - 4.76); P < 0.05 VIQ: 0.89 (- 2.87 to 4.65) Association between water fluoridation status and IQ scores with adjusting for MUF. – Breastfed FSIQ: - 1.69 (- 5.66 to 2.27) PIQ: - 6.30 (- 10.92 to - 1.68); P < 0.05 VIQ: 4.20 (- 0.06 to 8.45) – Formula-fed FSIQ: - 3.58 (- 7.83 to 0.66) PIQ: - 7.93 (- 12.84 to - 3.01); P < 0.05 VIQ: 2.60 (- 1.98 to 7.16) Association between fluoride intake from formula and IQ scores without adjusting for MUF. FSIQ: - 2.69 (- 7.38 to 2.01) PIQ: - 8.76 (- 14.18 to - 3.34); P < 0.05 VIQ: 3.08 (- 1.40 to 7.55) Association between fluoride intake from formula and IQ scores with adjusting for MUF. FSIQ: - 1.94 (- 7.09 to 3.21) PIQ: - 7.62 (- 13.64 to – 1.60); P < 0.05 VIQ: 3.05 (- 1.89 to 7.98)	
Wang et al., 2020[16]	
IQ scores – mean (SD): 106.74 (11.82); range: 75 to 145. 79.7% of the population had IQ scores between 90 and 120. Fluoride concentrations – mean (SD) – Water fluoride (mg/L): 1.39 (1.01); range: 0.20 to 3.90 – Urinary fluoride (mg/L): 1.28 (1.30); range 0.01 to 5.54 THs – mean (SD) – TT3 (ng/mL): 1.32 (0.19); range: 0.52 to 1.97 – FT3 (pg/mL): 3.28 (0.32); range: 1.58 to 4.46 – TT4 (µg/dL): 6.86 (1.16); range: 3.90 to 10.92 – FT4 (ng/dL): 1.13 (0.12); range: 0.83 to 1.58 – TSH (µIU/mL): 2.57 (1.29); range: 0.34 to 10.97 **Associations between fluoride exposure and THs – B (95% CI)** <u>Water fluoride</u>	*"Our study suggests low-moderate fluoride exposure is associated with alterations in childhood thyroid function that may modify the association between fluoride and intelligence."*[16] (p1)

Main Study Findings	Author's Conclusions
Quartile 2 (0.70 to 1.00 mg/L) versus Quartile 1 (≤ 0.70 mg/L) as reference – TT3 (mg/mL): - 0.029 (- 0.081 to 0.023); P = 0.275 – FT3 (pg/mL): - 0.017 (- 0.107 to 0.073); P = 0.719 – TT4 (μg/dL): - 0.376 (- 0.686 to - 0.066); P = 0.017 – FT4 (ng/dL): - 0.030 (- 0.063 to 0.003); P = 0.072 – TSH (μIU/mL): - 0.154 (- 0.517 to 0.209); P = 0.404 Continuous analyses by including all water fluoride levels of four quartiles ranging from 0.20 to 3.90 mg/L. The assessments of B (95% CI) for every 1 mg/L increment of water fluoride: – TT3 (mg/mL): 0.006 (- 0.001 to 0.022); P = 0.483 – FT3 (pg/mL): 0.013 (- 0.016 to 0.041); P = 0.382 – TT4 (μg/dL): - 0.083 (- 0.181 to 0.015); P = 0.097 – FT4 (ng/dL): - 0.010 (- 0.021 to 0.000); P = 0.054 – TSH (μIU/mL): 0.127 (0.014 to 0.241); P = 0.028 Urinary fluoride Quartile 2 (0.15 to 0.41 mg/L) versus Quartile 1 (≤ 0.15 mg/L) as reference – TT3 (mg/mL): 0.043 (- 0.001 to 0.087); P = 0.056 – FT3 (pg/mL): 0.051 (- 0.025 to 0.128); P = 0.188 – TT4 (μg/dL): 0.037 (- 0.231 to 0.305); P = 0.786 – FT4 (ng/dL): - 0.002 (- 0.030 to 0.026); P = 0.895 – TSH (μIU/mL): 0.019 (- 0.292 to 0.331); P = 0.904 Continuous analyses by including all urinary fluoride concentrations of four quartiles ranging from 0.01 to 5.54 mg/L. The assessments of B (95% CI) for every 1 mg/L increment of urinary fluoride: – TT3 (mg/mL): 0.007 (- 0.005 to 0.020); P = 0.233 – FT3 (pg/mL): 0.020 (- 0.001 to 0.042); P = 0.062 – TT4 (μg/dL): - 0.090 (- 0.164 to - 0.016); P = 0.017 – FT4 (ng/dL): - 0.009 (- 0.017 to - 0.002); P = 0.020 – TSH (μIU/mL): 0.110 (0.024 to 0.196); P = 0.013 **Associations between fluoride exposure and IQ scores – B (95% CI)** Water fluoride Quartile 2 (0.70 to 1.00 mg/L) versus Quartile 1 (≤ 0.70 mg/L) as reference – All: - 0.506 (- 3.764 to 2.753); P = 0.761 – Boys: 0.119 (- 4.540 to 4.777); P = 0.960 – Girls: - 1.134 (- 5.846 to 3.579); P = 0.636 Continuous analyses by including all water fluoride levels of four quartiles ranging from 0.20 to 3.90 mg/L. The assessments of B (95% CI) for every 1 mg/L increment of water fluoride: – All: - 1.587 (- 2.607 to - 0.568); P = 0.002 – Boys: -1.422 (- 2.792 to - 0.053); P = 0.042 – Girls: - 1.649 (- 3.201 to - 0.097); P = 0.037 Urinary fluoride Quartile 2 (0.15 to 0.41 mg/L) versus Quartile 1 (≤ 0.15 mg/L) as reference – All: - 0.342 (- 3.312 to 2.447); P = 0.810 – Boys: 1.094 (- 3.089 to 5.277); P = 0.607 – Girls: - 1.198 (- 5.171 to 2.771); P = 0.553 Continuous analyses by including all urinary fluoride concentrations of four quartiles ranging from 0.01 to 5.54 mg/L. The assessments of B (95% CI) for every 1 mg/L increment of urinary fluoride: – All: - 1.214 (- 1.987 to - 0.442); P = 0.002 – Boys: -1.037 (- 2.040 to - 0.035); P = 0.043 – Girls: - 1.379 (- 2.628 to - 0.129); P = 0.031	

Main Study Findings	Author's Conclusions
Associations between THs and IQ scores – B (95% CI) TT3 (ng/mL) Continuous analyses by including all TT3 concentrations ranging from 0.052 to 1.97 ng/mL. The assessments of B (95% CI) for every 1 ng/L increment of TT3. – All: 1.497 (- 4.049 to 7.044); P = 0.596 – Boys: 1.318 (- 6.215 to 8.887); P = 0.732 – Girls: 0.922 (- 7.558 to 9.402); P = 0.831 FT3 (pg/mL) Continuous analyses by including all FT3 concentrations ranging from 1.58 to 4.46 pg/mL. The assessments of B (95% CI) for every 1 pg/L increment of FT3. – All: 2.190 (- 0.899 to 5.368); P = 0.176 – Boys: 3.820 (- 0.544 to 8.184); P = 0.086 – Girls: 0.141 (- 4.643 to 4.926); P = 0.954 TT4 (µg/dL) Continuous analyses by including all TT4 concentrations ranging from 3.90 to 10.92 µg/dL. The assessments of B (95% CI) for every 1 µg/dL increment of TT4. – All: - 0.026 (- 0.944 to 0.892); P = 0.956 – Boys: - 0.761 (- 1.969 to 0.447); P = 0.216 – Girls: 0.572 (- 0.896 to 2.040); P = 0.444 FT4 (ng/dL) Continuous analyses by including all FT4 concentrations ranging from 0.83 to 1.58 ng/dL. The assessments of B (95% CI) for every 1 ng/dL increment of FT4. – All: 5.093 (- 3.568 to 13.772); P = 0.249 – Boys: 2.594 (- 9.283 to 14.472); P = 0.667 – Girls: 6.881 (- 6.381 to 20.142); P = 0.308 TSH (µIU/mL) Continuous analyses by including all TSH concentrations ranging from 0.34 to 10.97 µIU/mL. The assessments of B (95% CI) for every 1 µIU/mL increment of TSH. – All: - 0.406 (- 1.194 to 0.383); P = 0.312 – Boys: 0.149 (- 0.951 to 1.249); P = 0.790 – Girls: -0.942 (- 2.088 to 0.204); P = 0.107	
Riddell et al., 2019[18]	
Fluoride measurements – mean (SD) Urinary fluoride concentrations adjusted for specific gravity – Fluoridated areas: 0.82 (0.54) mg/L – Non-fluoridated areas: 0.46 (0.32) mg/L Water fluoride concentrations – Fluoridated areas: 0.49 (0.22) mg/L – Non-fluoridated areas: 0.04 (0.06) mg/L Comparison of youth with a urinary and water fluoride measurement with and without a diagnosis of ADHD – mean (SD) Urinary fluoride concentrations adjusted for specific gravity – ADHD diagnosis: 0.57 (0.32) mg/L – No ADHD diagnosis: 0.62 (0.45) mg/L Water fluoride concentrations – ADHD diagnosis: 0.29 (0.28) mg/L – No ADHD diagnosis: 0.22 (0.24) mg/L	*"Exposure to higher levels of fluoride in tap water is associated with an increased risk of ADHD symptoms and diagnosis of ADHD among Canadian youth, particularly adolescents. Prospective studies are needed to confirm these results."*[18] (p1)

Main Study Findings	Author's Conclusions
Assessment of ADHD and SDQ H/I subscale scores – 7.3% (137/1,877) of children were diagnosed with ADHD. – Mean SDQ H/I subscale scores: With ADHD diagnosis: 6.74 ± 2.5 Without ADHD diagnosis: 2.51 ± 2.4 **Association between fluoride exposure and ADHD diagnosis** – For every 1 mg/L increment of UF_{SG}, there was no significant association with ADHD diagnosis: OR (95% CI) = 0.96 (0.63 to 1.46) – For every 1 mg/L increment of water fluoride, there was a 6.1 times higher odds of ADHD diagnosis: OR (95% CI) = 6.10 (1.60 to 22.80) – Interaction between age and water fluoride was not significant. – CWF was associated with a 1.2 times higher odds of ADHD diagnosis: OR (95% CI) = 1.21 (1.03 to 1.42) – The association between CWF and ADHD diagnosis was significant at the 75th percentile of age (i.e., 14 years old): OR (95%CI) = 2.84 (1.40 to 5.76) – The association between CWF and ADHD diagnosis was not significant at the 25th percentile of age (i.e., 9 years old): OR (95%CI) = 0.91 (0.41 to 1.99) **Association between fluoride exposure and SDQ H/I subscale scores** – For every 1 mg/L increment of UF_{SG}, there was no significant association with SDQ H/I subscale scores: MD (95% CI) = 0.31 (-0.04 to 0.66) – For every 1 mg/L increment of water fluoride, there was a significant increase in SDQ H/I subscale scores by 0.31 points: MD (95% CI) = 0.31 (0.04 to 0.58) – The association between water fluoride and SDQ H/I subscale scores was significant at the 75th percentile of age (i.e., 14 years old): MD (95% CI) = 1.52 (0.23 to 2.80) – The association between water fluoride and SDQ H/I subscale scores was not significant at the 25th percentile of age (i.e., 9 years old): MD (95% CI) = - 0.33 (-1.51 to 0.84) – CWF was associated with 0.11 points increase in SDQ H/I subscale scores: MD (95% CI) = 0.11 (0.02 to 0.20) – The association between CWF and SDQ H/I subscale scores was significant at the 75th percentile of age (i.e., 14 years old): MD (95%CI) = 0.70 (0.34 to 1.06) – The association between CWF and SDQ H/I subscale scores was not significant at the 25th percentile of age (i.e., 9 years old): MD (95%CI) = 0.04 (-0.38 to 0.46)	

CI = confidence interval; CWF = community water fluoridation; FSIQ = full scale IQ; FT3 = free triiodothyronine; FT4 = free thyronine; IQ = intelligence quotient; MD = mean difference; MUF = maternal urinary fluoride; OR = odds ratio; PIQ = performance IQ; SD = standard deviation; SDQ H/I = Strengths ad Difficulties Questionnaire Hyperactivity-Inattention; THs = thyroid hormones; TSH = thyroid stimulating hormone; TT3 = total triiodothyronine; TT4 = total thyronine; VIQ = verbal IQ